COMMENT

The patient in the case here reported definitely had a toxic drug reaction. He ingested two drugs, Miltown and Transibarb. For the following reasons it is believed that the reaction was to Miltown: The patient noticed the onset of malaise, vertigo, flushing and yawning before he took Transibarb. The Transibarb capsule was taken because of the symptoms that developed after the ingestion of Miltown. There was no sudden change of the symptoms for the worse after the Transibarb was taken. Finally, the reaction was similar to reactions due to Miltown described by Selling.[3] Miltown is now being advocated for a wide range of diseases.[2,3] Few instances of toxicity following its use have been reported.

SUMMARY

A patient had severe toxic reaction following the ingestion of Miltown. This reaction consisted of vertigo, fever, syncope, erythema, purpura, and increased lymphocyte and platelet content in the blood. So far as is known, this is among the few reports of a severe reaction following the use of this drug.

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Untoward Reaction to Meprobamate (Equanil®)

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THE EXTREME PRESENT POPULARITY of the recently introduced ataraxic drug meprobamate* makes advisable wide dissemination of information concerning a severe and characteristic reaction which may appear as early as an hour after the first administration of the drug. A few instances of untoward reactions similar to the one herein described have already been recorded.[1,2,3,4,5]

REPORT OF A CASE

The patient, a 32-year-old white woman, ingested one 400 mg. tablet of Equanil® (meprobamate) for the first time, on May 28, 1956. Two hours later she noted a warm flushed feeling and a few moments later a red rash, beginning about the neck and rapidly spreading to involve the upper arms, axillae, chest and bathing trunk area. In addition, there was a feeling of faintness and some nausea. On examination four hours after onset of these symptoms the only significant physical abnormality was a bright red diffuse involvement of the skin in the areas mentioned, without appreciable edema, purpura or any urticarial component. A hemogram and results of urinalysis were normal.

The patient was given prednisone, 10 mg. orally every four hours, and rapid relief occurred; after two hours there was only mild erythema and slight itching of the groins and breasts and these symptoms disappeared within another day. A patch test of the skin for reaction to a crushed tablet of Equanil elicited some itching within 36 hours, but the visible reaction was so slight as to be doubtful.

To verify that meprobamate was the cause of the reaction, on June 20, 1956, the patient was asked to take a test dose of 100 mg. (one-fourth of a tablet). Instead she took an entire tablet. An hour later there was a recurrence, in more severe form, of the original reaction, with bright erythema of the same areas, six or seven brief fainting spells within a three-hour period, numbness of the legs, pronounced weakness, nausea and emotional upset described by the patient as "feeling ready to burst into tears." Relief was again achieved with prednisone, although more slowly than before.

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* Meprobamate is marketed by Wallace Laboratories under the trade name of Miltown, and by Wyeth, Inc., as Equanil.

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Postpartum Tetany and Psychosis Due to Hypocalcemia

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A 24-YEAR-OLD Mexican girl was brought to the emergency room of the hospital on March 10, 1955, at 5:30 p.m. because the family was concerned about her mental confusion which they said had been present for about three weeks. Vomiting and diarrhea had been present on and off for one week, diplopia for one day. The patient had delivered a normal infant on February 1, 1955. During the

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latter part of pregnancy she had had slight hypertension and mild albuminuria. When examined in the emergency room, the patient's temperature was normal; she was confused and disoriented but cooperative. Within a few minutes after admission she had a generalized tonic convulsion, then a clonic convulsion which lasted several minutes. The patient had not been taking insulin.

The tentative opinion was that she was having an epileptic form of seizure and symptomatic supportive therapy was given, including sodium Nembutal (pentobarbital) 0.25 gm., administered intravenously. The convulsion lasted about three to four minutes and was followed by deep coma.

Abnormalities noted upon complete examination were generalized flaccidity, small fixed pinpoint pupils, deviation of the right eye to the right and Babinski's reaction bilaterally. The patient was not perspiring and there was no nuchal rigidity. The blood pressure was 140 mm. of mercury systolic and 100 mm. diastolic.

It was the impression that the patient was in postepileptic coma, but in view of the extreme flaccidity a neurological lesion was contemplated, such as a spontaneous hemorrhage from a cerebral aneurysm or a brain tumor. Idiopathic hyperinsulinism, diabetic coma, postpartum eclampsia and uremia were also considered.

No abnormalities were noted on examination of the spinal fluid. A specimen of urine obtained by catheter showed no sugar, a trace of acetone, one-plus reaction for albumin and 20 to 30 hyaline casts per field. The hemoglobin content of the blood was 10.5 gm. per 100 cc. and erythrocytes numbered 4,150,000 per cu. mm. Leukocytes numbered 19,000 per cu. mm.—neutrophils 92 per cent, lymphocytes 8 per cent, blood platelets adequate.

Within an hour after admission the patient began to move and moan. Upon reexamination no nuchal rigidity was noted. The pupils were equal and reacted to light. The external ocular muscles and the optic fundi were normal. The heart and lungs were normal to auscultation. Tendon reflexes were normal. Babinski's sign was absent. Milk was draining freely from the breasts.

A satisfactory diagnosis had not yet been established. The abnormalities in the urine suggested uremia as the most likely possibility. However, the blood urea nitrogen, nonprotein nitrogen and carbon dioxide combining power were within normal limits.

About an hour and a half after the convulsion, the patient was conscious but slightly confused. Transient quivering and stiffness of the fingers of the right hand was noted. A Chvostek test elicited contraction of the upper and lower lips, and upon attempt to evoke Trousseau's sign a definite carpal spasm occurred.

These new signs taken together with the recent pregnancy and the fact that the patient had been nursing her child suggested postpartum hypocalcemia with acute tetany. Members of the family said that the patient had not taken calcium during pregnancy, had not ingested much milk and had eaten only small amounts of meat about twice weekly. The patient had never had any thyroid therapy or surgical operations. Further studies of the blood were ordered and the patient was given intravenous calcium therapy.

Results of laboratory determinations were as follows:

On admission: Serum calcium 7.05 mg., serum phosphorus 3.2 mg., nonprotein nitrogen 28.0 mg. and blood urea nitrogen 6.0 mg. per 100 cc.; carbon dioxide combining power 44 volumes per cent. A Sulkowitch test showed normal calcium excretion. Repeated follow-up examinations of the urine were within normal limits in all respects. Total serum protein was 5.6 gm., serum albumin 2.8 gm. and serum globulin also 2.8 gm. per 100 cc.

Two days later (March 12): Serum calcium was 8.1 mg. per 100 cc.

Four days after admission: Serum calcium was 8.25 mg. per 100 cc. and serum phosphorus 3.8 mg. per 100 cc. The result of a thymol turbidity test was 1.2 units (normal up to 4). Cephalin flocculation reaction was negative. A bromosulfalein retention test was within normal limits. A serologic test for syphilis was negative.

The patient was given a high protein diet, and 25 gm. of serum albumin was administered intravenously. Nine days after admission following vigorous calcium therapy, the serum calcium was 9.4 mg. per 100 cc. and serum phosphorus 3.8 mg. per 100 cc. The total serum protein on March 19, 1955, was 7.6 gm., albumin 4.0 gm. and globulin 3.6 gm. per 100 cc. X-ray films of the skeleton showed no evidence of abnormality attributable to nutritional deficiency.

Throughout the subsequent period of hospitalization the patient remained conscious and free of convulsive episodes. Generalized hyporeflexia continued for about 72 hours, as did Trousseau's and Chvostek's signs. As was indicated by the serial blood calcium studies previously mentioned, the biochemical response to specific therapy was satisfactory. However, the delusions and hallucinations for which medical aid was initially sought persisted and were further accentuated during the hospital stay. Calcium was administered both orally and parenterally in the form of calcium gluconate. A vitamin D preparation (Ertron, 5 mg. daily) was added to this regimen but was later supplanted by dihydrotachysterol capsules, 1 cc. three times a day. During the early part of the patient's hospitalization and prior to the return of serum calcium to a normal level, bouts of tachycardia were observed. An electrocardiogram showed low T waves in A V F and diphasic T waves in V_2 and V_3. The QT interval was within normal limits. An electroencephalogram showed no focal or general abnormalities.

The patient was transferred to the psychopathic unit of the Los Angeles County General Hospital on the ninth day after admission, since mental symp-

toms had deteriorated to the point of violently disturbed behavior requiring psychiatric institutional care.

Improvement was noted after one month and the patient was discharged as mentally cured two months after onset. An electrocardiogram taken eight months later showed no change from the previous one except for an upright TV_3.

REVIEW OF LITERATURE

In 1830 Steinheim[8] reported a case of tetany associated with pregnancy and lactation. Kehver[6] in 1913 observed that the Chvostek sign was present in 75 per cent of all pregnant women. In an extensive review of the literature on tetany in relation to pregnancy, Anderson and Musselman[1] tabulated cases of idiopathic tetany, tetany associated with lactation, tetany associated with thyroid disease, tetany following thyroidectomy, tetany during pregnancy, tetany during delivery, tetany due to low calcium intake, exacerbation of tetany with menses, tetany with psychic changes and bilateral cataracts, and tetany due to loss of blood.

Maternal tetany with or without psychosis aroused widespread interest in the medical profession for the first time in the middle of the 19th century. Trousseau's name, so intimately connected with the present-day concept of tetany, was originally linked to this type of tetany to the exclusion of all other forms. The name of Trousseau's first treatise[9] on the subject of tetany was "Contractures des Nourrices." In that treatise Trousseau reported observing in mothers with suckling infants the well-known phenomenon to which his name is attached. Having observed an "epidemic" of such "nursing contractures" at that time, he was led to believe that this was the most common form of tetany. Trousseau later realized the considerably broader aspects of tetany.

Frankl-Hochwart[4] at the beginning of this century was the first to contribute a comprehensive and critical summary of the subject of tetany; and he described in detail case histories of the various aspects of the syndrome. With regard to maternal tetany he collected reports of 53 cases from the then existing literature and added 23 cases he had observed, making a total of 76. Frankl-Hochwart also observed epidemics of the various types of tetany occurring in certain groups of individuals at certain times of the year. He emphasized that the most outstanding common single factor among cases of maternal tetany was seasonal occurrence in the late winter and early spring. Three out of four cases of maternal tetany in the series he reported upon occurred between the months of January and April. The majority of patients belonged to the lower income groups. About 10 per cent of the patients in the series had symptoms of psychosis of a toxic metabolic type which in no way differed from postpartum psychosis not ascribable to any specific cause.

Greene and Swanson[5] noted that in five of 18 patients with hypoparathyroidism a psychosis developed which took up to a month to improve. They described no specific type of psychosis in tetany, but a "toxic" type of delirium predominated, with delusions and hallucinations. They observed that sexual hallucinations, delusions of persecution, mental depression and tendency to suicide occurred. The psychic manifestations they noted, may be present only temporarily during and following a convulsion or they may persist for several months. The prognosis is usually good but the mental recovery is usually delayed one or more months after the serum calcium becomes normal. The cause of the psychosis is not known.

DISCUSSION

The differential diagnosis in the case of a female patient having generalized convulsions should include epilepsy, alkalosis due to hyperventilation, hypoglycemia, meningitis, tetanus, eclampsia, uremia, strychnine poisoning, brain tumor, cerebrovascular accident, and hypocalcemia. The latter can be due to a low calcium intake, negative calcium balance as seen in pregnancy and lactation, hypoparathyroidism either spontaneous or following the removal of a parathyroid tumor or after total thyroidectomy. Low serum calcium also occurs in so-called renal rickets where, because of renal insufficiency, the excretion of phosphates is impaired, causing a rise in serum phosphorus.[3] This causes a decrease in serum calcium, probably due to the precipitation of insoluble calcium phosphate in the intestines. If the serum calcium levels become low enough, tetany and convulsions may occur. However, these complications are somewhat blocked by the coexistent acidosis.

The hypocalcemia in the case herein reported was the result of pregnancy, lactation and low calcium and low protein intake.

According to Best and Taylor[2] over 60 per cent of the skeletal calcium of the newborn is deposited during the last two months of prenatal life. However, the greatest loss of maternal calcium is to the suckling child, amounting to over 80 gm. secreted during a normal period of lactation (nine months) compared to 20 gm. of calcium lost during pregnancy. At the time of the convulsion the patient in the present case was five weeks postpartum; she was nursing her infant and had a heavy flow of milk. She had not taken the prescribed calcium supplement, she did not drink milk or milk products, and her protein intake (meat) was inadequate.

Protein foods tend to increase the absorption of calcium, since the latter forms soluble complexes with certain amino acids. Of the total serum calcium about 45 per cent appears to be bound by protein (nondiffusible), with the remainder present as calcium ions (diffusible). The nondiffusible calcium varies with the protein concentration of the plasma. Calcium concentrations are usually lower with hypoalbuminemia; the globulin factor has a lesser effect.

The carbon dioxide combining power in the present case was 44 volumes per cent, which is almost a normal level. This may have had a tendency to aggravate the tetany tendency as the serum ionized calcium is probably increased in acidosis and decreased in alkalosis. The patient's vomiting and diarrhea were probably due to a nonspecific gastroenteritis and may have had some effect on the level of the carbon dioxide combining power.

Did this patient have hypoparathyroidism or postpartum psychosis? She had not had either a thyroid or parathyroid operation, which is the usual cause of parathyroprivic tetany. However, spontaneously arising cases have been reported.[7] In hypoparathyroid patients the serum calcium is low, phosphorus is high and carbon dioxide combining power essentially normal. In patients with low calcium intake and/or lactation, the calcium is low and the phosphorus low or normal, as it was in the present case. The reported cases in the literature do not always clearly differentiate these two types of tetany, especially in relation to psychosis, hypocalcemia and lactation.

The onset of postpartum psychosis is within two to three weeks after delivery in four-fifths of the cases. There is usually some evidence of previous psychotic episodes and frequently there is some activating mental and physical stress such as prolonged labor, hemorrhage, puerperal infection, elderly primiparity, anemia, toxemia or constitutional psychopathic background. The onset in this case was five weeks postpartum, with malnutrition and possibly hyperlactation as stress factors.

Psychoses that occur in association with well-differentiated somatic disorders are of interest because of the opportunities they offer of correlating mental manifestations with tangible pathological factors. This is particularly true of the psychoses associated with disorders of metabolism. The clinical manifestations and the significant depression of the blood calcium level together with the history of poor dietary intake and superimposed lactation, can certainly not be disregarded in the course of the self-limited "postpartum psychosis" of the patient in the case herein reported. There is no reason to believe that there is a specific tetany psychosis. However, the muscular disturbances of a neurological nature and the psychosis are both the result of a toxic process affecting the central nervous system.

TREATMENT

Treatment was directed toward correcting the calcium and protein deficiency by giving calcium intravenously at the outset and then orally, and by a high protein diet. A small amount (25 gm.) of albumin was given intravenously. Vitamin supplements, especially vitamin D, were also administered. Dihydrotachysterol was given to increase the intestinal absorption of calcium but its effect in patients with other than hypoparathyroidism is probably not needed.

SUMMARY

A case of hypocalcemia in a lactating mother who had been on a deficient calcium and protein diet is presented. The patient had psychosis, tetany and generalized convulsions, all of which responded to calcium therapy.

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